=> fil reg

FILE 'REGISTRY' ENTERED AT 17:07:44 ON 04 OCT 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 3 OCT 2000 HIGHEST RN 292600-11-4
DICTIONARY FILE UPDATES: 3 OCT 2000 HIGHEST RN 292600-11-4

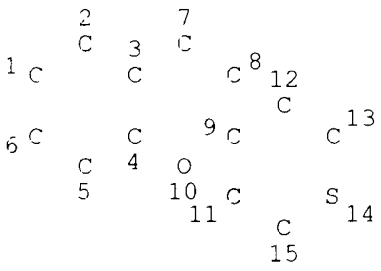
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 11, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> d sta que l57

L54 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

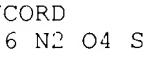
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

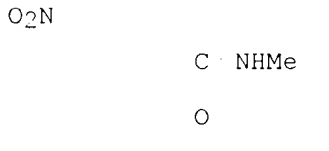
STEREO ATTRIBUTES: NONE
L56 52 SEA FILE=REGISTRY SSS FUL L54
L57 2 SEA FILE=REGISTRY ABB=ON PLU=ON L56 AND OC5-SC5-C6/ES

=> d ide can tot l57

L57 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 153382-99-1 REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-[4H]thiopyran] (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C13 H10 O S
CI RPS
SR CA Index Guide or Ring Systems Handbook

L57 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 152661-12-6 REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-[4H]thiopyran]-4-carboxamide,
2',3',5',6'-tetrahydro-N-methyl-6-nitro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C15 H16 N2 O4 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL





1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:106765

=> fil beil

FILE 'BEILSTEIN' ENTERED AT 17:08:02 ON 04 OCT 2000
COPYRIGHT (c) 2000 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften
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FILE LAST UPDATED: 6 MAR 2000

FILE COVERS 1779 TO 2000.
*** CAS REGISTRY NUMBERS FOR 4,356,237 SUBSTANCES AVAILABLE ***
*** FILE CONTAINS 7,688,486 SUBSTANCES ***

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**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE   *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE          *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                        *
* FOR PRICE INFORMATION SEE HELP COST                                *
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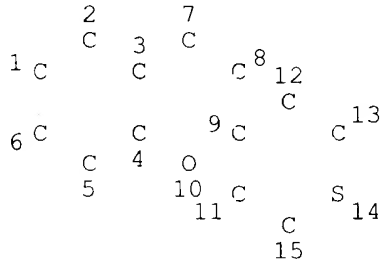
=> d sta que

L54 STR

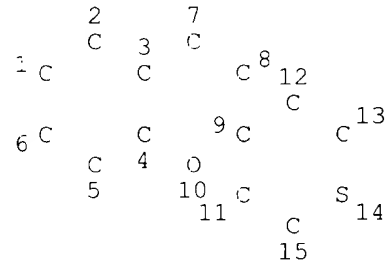


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L59 4 SEA FILE=BEILSTEIN SSS FUL L54
L60 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L62 0 SEA FILE=BEILSTEIN SUB=L59 SSS FUL L60

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.02

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 17:08:10 ON 04 OCT 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1967 - 4 Oct 2000 VOL 133 ISS 15
FILE LAST UPDATED: 3 Oct 2000 (20001003/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGistRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=> s 157

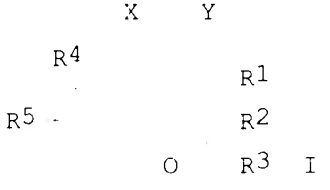
L63 1 L57

=> d all

L63 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:106765 HCAPLUS
DN 120:106765
TI Preparation of benzopyran derivatives having potassium ion channel activating activity
IN Koga, Hiroshi; Nabata, Hiroyuki
PA Chugai Seiyaku K. K., Japan
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07D311-58
ICS A61K031-35
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9315068	A1	19930805	WO 1993-JP86	19930125
W: AT, AU, BR, CA, CH, DE, ES, GB, HU, LU, MG, MN, NL, NO, NZ, PL, PT, RO, RU, SD, SE, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
ZA 9300436	A	19930825	ZA 1993-436	19930121
CN 1077954	A	19931103	CN 1993-102056	19930122
CN 1036918	B	19980107		
JP 05294954	A2	19931109	JP 1993-9421	19930122
AU 9333673	A1	19930901	AU 1993-33673	19930125
EP 632033	A1	19950104	EP 1993-902526	19930125
EP 632033	B1	19990407		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 178601	E	19990415	AT 1993-902526	19930125
ES 2132217	T3	19990816	ES 1993-902526	19930125
US 5646308	A	19970708	US 1994-256580	19940718
PRAI JP 1992-10819	19920124			
WO 1993-JP86	19930125			

OS MARPAT 120:106765
GI



AB The title compds. [I; R1 = H, OH; R2, R3 = (halo or lower alkoxy-substituted) lower alkyl, or R1R2 forms a heterocyclic ring having O or S atom; provided that both R1 and R2 are not simultaneously lower alkyl; R4, R5 = H, lower (halo)alkyl, halo, lower (halo)alkoxy, amino, acylamino, NO2, cyano, ester group, lower alkylsulfonyl, arylsulfonyl; X = O, S, NZ; Z = H, lower alkyl, aryl, OH, lower alkoxy, cyano, CONH2, SO2NH2; Y = NR6R7, OR8, SR9; R6, R7 = H, OH, lower alkoxy, cyano, (un)substituted NH2 or (un)satd. lower alkyl, (un)substituted

(hetero)aryl, or cycloalkyl; R8, R9 = H, lower alkyl, aryl], useful as antiasthmatic and antiepileptic agents, are prepd. Addn. of 2,2-bis(fluoromethyl)-3,4-dihydro-6-nitro-2H-1-benzopyran-4-one with Me3SiCN in benzene contg. Et2Zn followed by refluxing with pyridine and P(O)Cl3 and hydrolysis of the resulting 4-cyano-2,2-bis(fluoromethyl)-6-nitro-2H-1-benzopyran with concd. H2SO4-H2O-AcOH to give 2,2-bis(fluoromethyl)-6-nitro-2H-1-benzopyran-4-carboxylic acid. Treatment of the latter with carbonyl diimidazole in THF followed by amidation with MeNH2 and sulfurization of the resulting 2,2-bis(fluoromethyl)-6-nitro-2H-1-benzopyran-4-carboxamide (II) with Lawesson's reagent in refluxing benzene gave 2,2-bis(fluoromethyl)-6-nitro-2H-1-benzopyran-4-thiocarboxamide (III). II and III showed IC50 of 6.0 .times. 10-9 and 2.8 .times. 10-10 M, resp., for inhibiting the KCl-induced contraction of rat's aortas. II showed ED50 of 0.01 mg/kg for inhibiting the histamine-induced increase in the inner pressure of guinea pig's respiratory tracts vs. 1.0-3.0 mg/kg for cromakalim.

ST benzopyran prepn potassium ion channel activator; antiasthmatic antiepileptic benzopyran

IT Anticonvulsants and Antiepileptics
(benzopyran derivs.)

IT Bronchodilators
(antiasthmatics, benzopyran derivs.)

IT Ion channel
(potassium, activators, benzopyran derivs.)

IT 147402-35-5P 152661-50-2P 152661-51-3P 152661-52-4P 152661-53-5P
152661-54-6P 152661-55-7P 152661-56-8P 152661-57-9P 152661-58-0P
152661-59-1P 152661-60-4P 152661-61-5P 152661-62-6P 152661-63-7P
152661-64-8P 152661-65-9P 152661-66-0P 152661-67-1P 152661-68-2P
152661-69-3P 152661-70-6P 152661-71-7P 152661-72-8P 152661-73-9P
152661-74-0P 152661-75-1P 152661-76-2P 152661-77-3P 152661-78-4P
152661-79-5P 152661-80-8P 152661-81-9P 152661-82-0P 152661-83-1P
152661-84-2P 152661-85-3P 152661-86-4P 152661-87-5P 152661-88-6P
152661-89-7P 152661-90-0P 152661-91-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for potassium ion channel activator benzopyran deriv.)

IT 147402-26-4P 147402-31-1P 147402-33-3P 152661-01-3P 152661-02-4P
152661-03-5P 152661-04-6P 152661-05-7P 152661-06-8P 152661-07-9P
152661-08-0P 152661-09-1P 152661-10-4P 152661-11-5P
152661-12-6P 152661-13-7P 152661-14-8P 152661-15-9P
152661-16-0P 152661-17-1P 152661-18-2P 152661-19-3P 152661-20-6P
152661-21-7P 152661-22-8P 152661-23-9P 152661-24-0P 152661-25-1P
152661-26-2P 152661-27-3P 152661-28-4P 152661-29-5P 152661-30-8P
152661-31-9P 152661-32-0P 152661-33-1P 152661-34-2P 152661-35-3P
152661-36-4P 152661-37-5P 152661-38-6P 152661-39-7P 152661-40-0P
152661-41-1P 152661-42-2P 152661-43-3P 152661-44-4P 152661-45-5P
152661-46-6P 152661-47-7P 152661-48-8P 152661-49-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as potassium ion channel activator)

IT 74-88-4, Methyl iodide, reactions 74-89-5, Methylamine, reactions 75-03-6, Ethyl iodide 151-18-8, 2-Cyanoethylamine 378-76-7, Potassium pentafluoropropionate 420-04-2, Cyanamide 423-39-2, Nonafluorobutyl iodide 544-92-3, Copper(I) cyanide 556-61-6, Methyl isothiocyanate 2923-16-2, Potassium trifluoroacetate 2966-54-3, Potassium heptafluorobutyrate 7677-24-9, Trimethylsilyl cyanide 7681-11-0, Potassium iodide, reactions 7758-89-6, Copper(I) chloride 147402-37-7 152661-92-2 152661-93-3 152661-94-4 152661-95-5 152661-96-6 152661-97-7 152661-98-8
RL: RCT (Reactant)
(reaction of, in prepn. of potassium ion channel activator benzopyran deriv.)

=> fil reg

FILE 'REGISTRY' ENTERED AT 17:08:24 ON 04 OCT 2000

STRUCTURE FILE UPDATES: 3 OCT 2000 HIGHEST RN 292600-11-4
DICTIONARY FILE UPDATES: 3 OCT 2000 HIGHEST RN 292600-11-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 11, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

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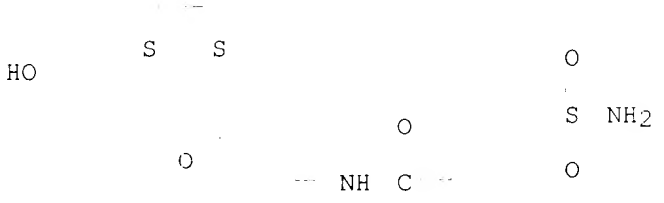
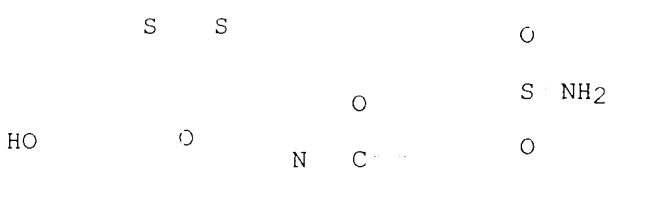
L49 ANSWER 1 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-77-7** REGISTRY
CN Benzamide, 4-(aminosulfonyl)-N-(6'-hydroxydispiro[cyclohexane-1,2'-[2H-1]benzopyran-4'(3'H),2''-[1,3]dithiolan]-4-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C23 H26 N2 O5 S3**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:202020

L49 ANSWER 2 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-76-6** REGISTRY
CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),4''-piperidin]-7'-ol, 1''-[4-(aminosulfonyl)benzoyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H24 N2 O5 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

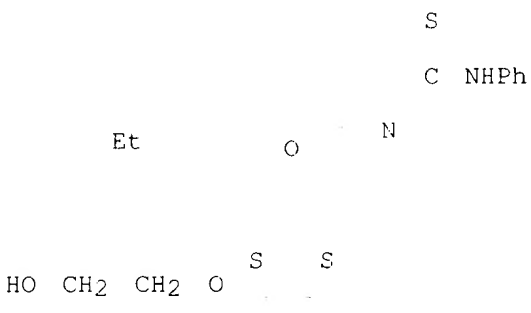


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 3 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-75-5** REGISTRY
CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),3''-pyrrolidine]-1''-carbothioamide, 7'-ethyl-5'-(2-hydroxyethoxy)-4-methyl-N-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H32 N2 O3 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

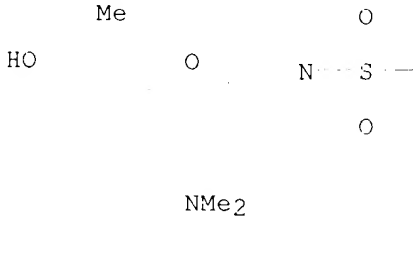


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 4 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-74-4** REGISTRY
CN Spiro[2H-1-benzopyran-2,3'-pyrrolidin]-7-ol, 4-(dimethylamino)-3,4-dihydro-8-methyl-1'-(2-naphthalenylsulfonyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C25 H28 N2 O4 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



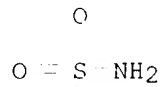
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

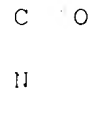
REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 5 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-73-3** REGISTRY

CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),3''-pyrrolidin]-6'-ol, 1''-[4-(aminosulfonyl)benzoyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H22 N2 O5 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



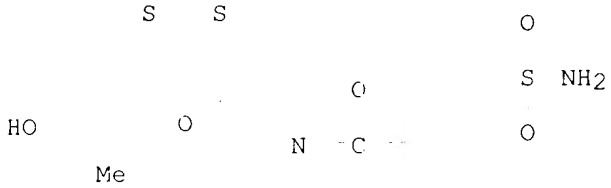


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 6 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-72-2** REGISTRY
CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),4''-piperidin]-7'-ol, 1''-[4-(aminosulfonyl)benzoyl]-8'-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H26 N2 O5 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



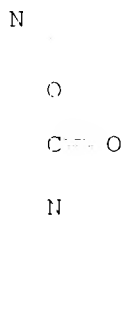
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

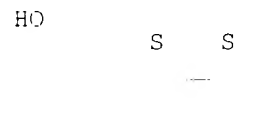
REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 7 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-71-1** REGISTRY
CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),3''-pyrrolidine]-1''-carboxylic acid, 6'-hydroxy-, 2-pyridinyl ester (9CI) (CA INDEX NAME)

FS 3D CONCORD
MF **C20 H20 N2 O4 S2**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



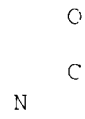


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 8 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-70-0** REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one, 6-hydroxy-1'-(phenylacetyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C21 H21 N O4**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



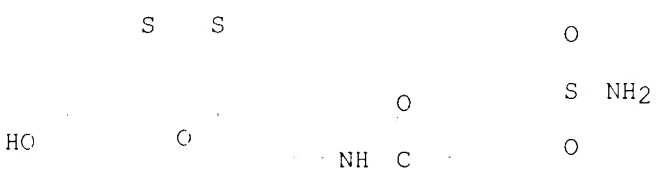
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 9 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-69-7** REGISTRY
CN Benzamide, 4-(aminosulfonyl)-N-(7'-hydroxydispiro[cyclohexane-1,2'-[2H-1]benzopyran-4'(3'H),2''-[1,3]dithiolan]-4-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C23 H26 N2 O5 S3**

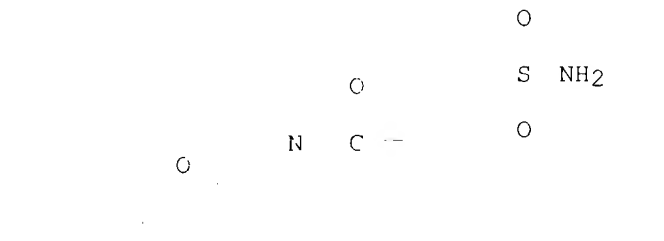
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:202020

L49 ANSWER 10 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-68-6** REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one, 1'-[4-(aminosulfonyl)benzoyl]-6-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C20 H20 N2 O6 S**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

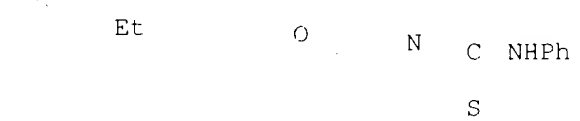


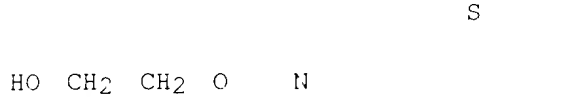
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 11 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-67-5** REGISTRY
CN Spiro[2H-1-benzopyran-2,3'-pyrrolidine]-1'-carbothioamide, 7-ethyl-3,4-dihydro-5-(2-hydroxyethoxy)-N-phenyl-4-(1-piperidinyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C28 H37 N3 O3 S**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



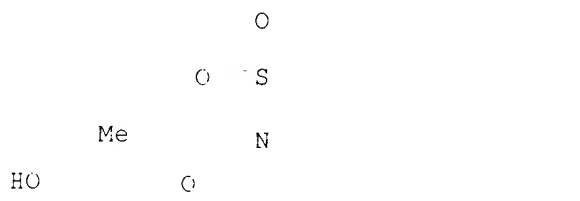


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 12 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-66-4** REGISTRY
CN Spiro[2H-1-benzopyran-2,3'-piperidin]-7-ol, 4-(1,1-dioxido-4-thiomorpholinyl)-3,4-dihydro-8-methyl-1'-(2-naphthalenylsulfonyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H32 N2 O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

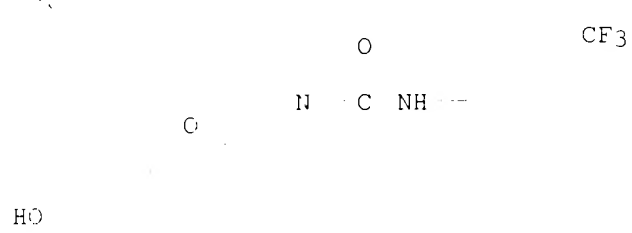


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 13 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-65-3** REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-piperidine]-1'-carboxamide, 3,4-dihydro-4,6-dihydroxy-N-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C21 H21 F3 N2 O4**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

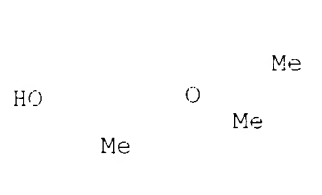


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 14 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-64-2** REGISTRY
CN Spiro[4H-1-benzopyran-4,2'-[1,3]dithiolan]-7-ol, 2,3-dihydro-2,2,8-trimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H18 O2 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

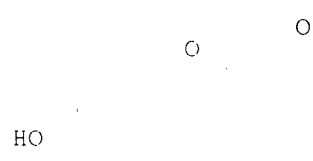


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 15 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-63-1** REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-[4H]pyran]-4(3H)-one, 2',3',5',6'-tetrahydro-6-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C13 H14 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

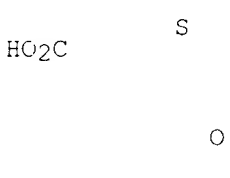


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 16 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-62-0** REGISTRY
CN Dispiro[cycloheptane-1,2'-[2H-1]benzopyran-4'(3'H),2''-[1,3]dithiolane]-6'-carboxylic acid, 8'-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C19 H24 O3 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

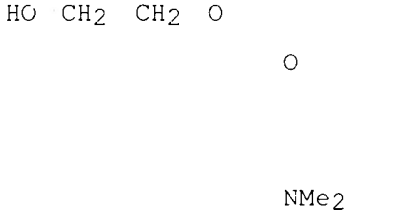


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 17 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-61-9** REGISTRY
CN Ethanol, 2-[[4-(dimethylamino)-3,4-dihydrospiro[2H-1-benzopyran-2,1'-cyclohexan]-8-yl]oxy]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C18 H27 N O3**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



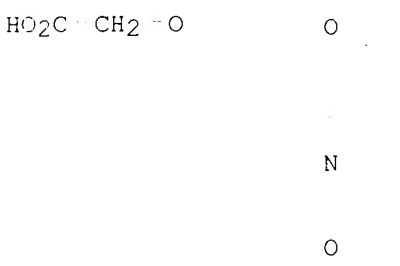
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 18 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-60-8** REGISTRY
CN Acetic acid, [[3,4-dihydro-4-(4-morpholinyl)spiro[2H-1-benzopyran-2,1'-cyclopentan]-7-yl]oxy]- (9CI) (CA INDEX NAME)
FS 3D CONCORD

MF **C19 H25 N O5**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

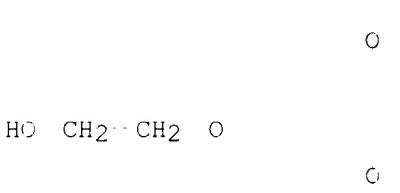


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 19 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-59-5** REGISTRY
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-6-(2-hydroxyethoxy)-2-methyl-2-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C15 H20 O4**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

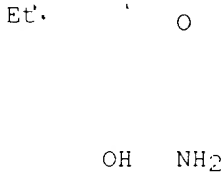


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 20 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-58-4** REGISTRY
CN 2H-1-Benzopyran-5-ol, 4-amino-2,7-diethyl-3,4-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C13 H19 N O2**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

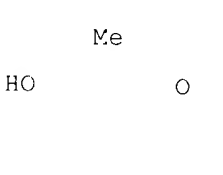


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 21 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-57-3** REGISTRY
CN 2H-1-Benzopyran-4,7-diol, 3,4-dihydro-2,2,8-trimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C12 H16 O3**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

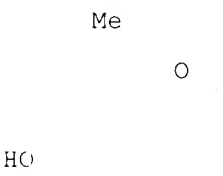


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 22 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-56-2** REGISTRY
CN 2H-1-Benzopyran-4,6-diol, 2,2-diethyl-3,4-dihydro-8-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C14 H20 O3**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

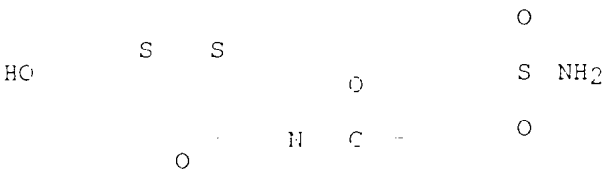


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

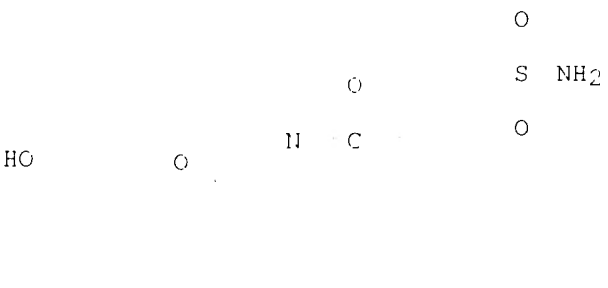
L49 ANSWER 23 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-54-0** REGISTRY
CN Dispiro[1,3-dithiolane-2,4'-[4H-1]benzopyran-2'(3'H),3''-piperidin]-6'-ol, 1''-[4-(aminosulfonyl)benzoyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H24 N2 O5 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:202020

L49 ANSWER 24 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **174300-53-9** REGISTRY
CN Spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one, 1'-[4-(aminosulfonyl)benzoyl]-7-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C20 H20 N2 O6 S**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

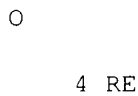
REFERENCE 1: 127:17591

REFERENCE 2: 124:202020

L49 ANSWER 25 OF 25 REGISTRY COPYRIGHT 2000 ACS
RN **135110-68-8** REGISTRY
CN Spiro[2H-1-benzopyran-2,1'-cyclohexan]-4(3H)-one, 6-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C14 H16 O3**
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

HO



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:296585

REFERENCE 2: 127:17591

REFERENCE 3: 124:202020

REFERENCE 4: 115:71398

=> fil hcaplus

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FILE COVERS 1967 - 4 Oct 2000 VOL 133 ISS 15
FILE LAST UPDATED: 3 Oct 2000 (20001003/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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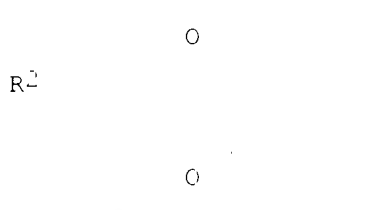
=> s l49

L64 4 L49

=> d all tot

L64 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:204265 HCAPLUS
DN 130:296585
TI Synthesis of some 2-substituted 4-chromanones utilizing o-hydroxyacetophenones
AU Cascaval, Alexandru; Finaru, Adriana; Prisecaru, Maria
CS Faculte de Chimie, Universite "A.I. Cuza" - Iasi, Iasi, Rom.

SO Rev. Roum. Chim. (1998), 43(8), 747-751
CODEN: RRCHAX; ISSN: 0035-3930
PB Editura Academiei Romane
DT Journal
LA French
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 5
GI



I

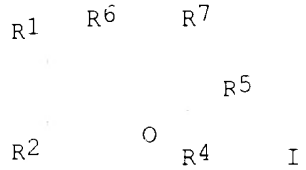
AB Title compds. I (R1 = H, R2 = OH, Br; R1 = R2 = Br) were prepd. from 2'-hydroxyacetophenones. I (R1 = H, R2 = OH) was converted to its acetate and benzenesulfonate esters. Biol. activity tests of the synthesized compds. were performed on Fundulea 29 wheat (Triticum aestivum L) specimens.
ST chromanone deriv prepn pesticide
IT Pesticides
(chromanone spiro derivs.)
IT Cyclocondensation reaction
(of 2'-hydroxyacetophenones with cyclohexanone)
IT 108-94-1, Cyclohexanone, reactions
RL: RCT (Reactant)
(cyclocondensation with 2'-hydroxyacetophenones)
IT 490-78-8, 2',5'-Dihydroxyacetophenone 1450-75-5, 5'-Bromo-2'-hydroxyacetophenone 22362-66-9, 2'-Hydroxy-3',5'-dibromoacetophenone
RL: RCT (Reactant)
(cyclocondensation with cyclohexanone)
IT 223416-26-0P 223416-27-1P 223416-29-3P 223416-30-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and bioactivity of)
IT **135110-68-8P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., acylation, and bioactivity of)
RE.CNT 5
RE
(1) Cascaval, A; Synthesis 1983, V4, P579
(2) Cascaval, A; Synthesis 1984, V2, P277
(3) Kabbe, H; Justus Liebigs Ann Chem 1976, P511 HCAPLUS
(4) Kabbe, H; Synthesis 1978, P888 HCAPLUS
(5) Lockhart, J; J Med Chem 1972, V15, P863

L64 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:403189 HCAPLUS
DN 127:17591
TI Preparation of benzopyrans as drugs and combinatorial libraries containing them
IN Baldwin, John J.; Dillard, Lawrence W.; Li, Ge; Reader, John C.; Zeng, Wenguang
PA Pharmacopeia, Inc., USA
SO PCT Int. Appl., 165 pp.
CODEN: PIXXD2
DT Patent
LA English

IC ICM G01N033-53
ICS G01N033-543; G01N033-551; G01N033-553; G01N033-567; C12Q001-34
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9716729	A1	19970509	WO 1996-US17982	19961104
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5821130	A	19981013	US 1995-552698	19951103
	AU 9676750	A1	19970522	AU 1996-76750	19961104
	EP 864087	A1	19980916	EP 1996-939617	19961104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1995-552698	19951103			
	US 1994-239302	19940506			
	US 1995-436120	19950508			
	US 1996-733803	19961018			
	WO 1996-US17982	19961104			

OS MARPAT 127:17591
GI



AB Title benzopyrans (I; R1 = OH, OCH2OH, OCH2CO2H, etc.; R2 = H or alkyl; R4,R5 = H, alkyl, piperazinoalkyl, etc.; R4R5 = alkylene, CH2CH2OCH2CH2, CH2CH2NR8CH2CH2, etc.; 1 of R6,R7 = H and the other = H, OH, alkylamino, etc.; R6R7 = O, SCH2CH2S, OCH2CH2O, etc.; R8 = H, alkoxycarbonyl, alkylcarbamoyl, alkanoyl, etc.) were claimed as carbonic anhydrase inhibitors (no data) and as components of bead-linked combinatorial libraries.
ST benzopyran prepn drug combinatorial library; carbonic anhydrase inhibitor benzopyran prepn
IT Combinatorial library
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 9001-03-0, Carbonic anhydrase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibitors; prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT **135110-68-8P 174300-53-9P 174300-56-2P**
174300-57-3P 174300-58-4P 174300-59-5P
174300-60-8P 174300-61-9P 174300-62-0P
174300-63-1P 174300-64-2P 174300-65-3P
174300-66-4P 174300-67-5P 174300-68-6P
174300-70-0P 174300-71-1P 174300-72-2P
174300-73-3P 174300-74-4P 174300-75-5P
174300-76-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzopyrans as drugs and combinatorial libraries contg.

them)
IT 89-84-9 107-18-6, Allyl alcohol, reactions 2393-23-9, 4-Methoxybenzylamine 3943-74-6, Methyl vanillate 24424-99-5, Di-tert-butyl dicarbonate 55715-03-2, 3-Nitro-4-bromomethylbenzoic acid 82379-38-3, 4-Hydroxymethyl-3-nitrobenzoic acid 96965-31-0, tert-Butyl 4-acetoxymethyl-3-nitrobenzoate 156459-80-2, 9-Pentachlorophenoxy-1-nonanol
RL: RCT (Reactant)
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 65276-91-7P 89950-93-6P 156459-64-2P 156459-74-4P 171762-24-6P 174300-79-9P 174300-81-3P 174300-82-4DP, resin-bound 174300-82-4P 190602-46-1DP, resin-bound 190602-47-2DP, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)

L64 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:153421 HCAPLUS
DN 124:202020
TI Combinatorial dihydrobenzopyran library
IN Baldwin, John J.; Reader, John C.; Dillard, Lawrence W.; Burbaum, Jonathan J.; Zeng, Wenguang; Li, Ge
PA Pharmacopeia, Inc., USA
SO PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C205-06
ICS C07D311-04; C07D279-10; C07D275-02; C07D207-00; A61K031-555; A61K031-54; A61K031-50; A61K031-385; A61K031-35
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 6

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9530642	A1	19951116	WO 1995-US5940	19950508
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2189634	AA	19951116	CA 1995-2189634	19950508
AU 9525869	A1	19951129	AU 1995-25869	19950508
AU 691296	B2	19980514		
EP 758313	A1	19970219	EP 1995-920411	19950508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10500112	T2	19980106	JP 1995-529207	19950508
PRAI US 1994-239302	19940506			
WO 1995-US5940	19950508			

OS MARPAT 124:202020
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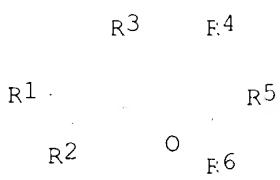

AB Combinatorial libraries, represented by divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene-supported reagents, contain dihydrobenzopyrans I [R1 = OH, OCH2CO2H, CO2H, etc.; R2 = H, alkyl; R3 = R4 = H, R3 = H, R4 = OH, R3R4 = -SCH2CH2S-, etc.; R5, R6 = H,

(substituted) alkyl, aryl, etc.] which interact (i.e., as agonists or antagonists) with .alpha. adrenergic receptors, dopamine receptor, .sigma.-opiate receptors, and K+ channels and are inhibitors of carbonic anhydrase isoenzymes. They are useful in the treatment of ocular diseases such as glaucoma. Compds. I are effective at 0.1-1.0 mg/kg per day in humans.

ST dihydrobenzopyran combinatorial library; adrenergic agonist antagonist dihydrobenzopyran combinatorial library; dopamine agonist antagonist dihydrobenzopyran combinatorial library; opiate agonist antagonist dihydrobenzopyran combinatorial library; carbonic anhydrase inhibitor dihydrobenzopyran combinatorial library; ocular disease dihydrobenzopyran combinatorial library; glaucoma dihydrobenzopyran combinatorial library

IT Combinatorial library
Eye, disease
Glaucoma (disease)
Polymer-supported reagents
(dihydrobenzopyran pharmaceuticals)

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.sigma.-, agonist-antagonist; dihydrobenzopyran pharmaceuticals)

IT Neurotransmitter agonists
Neurotransmitter antagonists
(dopaminergic, dihydrobenzopyran pharmaceuticals)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(opioid, .sigma.-, agonist-antagonist; dihydrobenzopyran pharmaceuticals)

IT Ion channel blockers
Ion channel openers
(potassium, dihydrobenzopyran pharmaceuticals)

IT Adrenergic agonists
Adrenergic antagonists
(.alpha.-, dihydrobenzopyran pharmaceuticals)

IT **135110-68-8P 174300-53-9P 174300-54-0P**
174300-55-1P **174300-56-2P 174300-57-3P**
174300-58-4P 174300-59-5P 174300-60-8P
174300-61-9P 174300-62-0P 174300-63-1P
174300-64-2P 174300-65-3P 174300-66-4P
174300-67-5P 174300-68-6P 174300-69-7P
174300-70-0P 174300-71-1P 174300-72-2P
174300-73-3P 174300-74-4P 174300-75-5P
174300-76-6P 174300-77-7P 174300-78-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dihydrobenzopyran pharmaceuticals)

IT 89-84-9 107-18-6, 2-Propen-1-ol, reactions 2393-23-9, 4-Methoxybenzylamine 3943-74-6, Methyl vanillate 24424-99-5, Di-tert-butyl dicarbonate 55715-03-2, 3-Nitro-4-(bromomethyl)benzoic acid 82379-38-2, 4-Hydroxymethyl-3-nitrobenzoic acid 96965-31-0 156459-80-2
RL: RCT (Reactant)
(dihydrobenzopyran pharmaceuticals)

IT 65276-91-7P 156459-74-4P 171762-24-6P 174300-80-2P 174300-81-3P 174300-82-4P 174300-83-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(dihydrobenzopyran pharmaceuticals)

IT 89950-93-6P 156459-64-2P 174300-79-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(dihydrobenzopyran pharmaceuticals)

IT 9001-03-0, Carbonic anhydrase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; dihydrobenzopyran pharmaceuticals)

L64 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:471398 HCAPLUS

DN 115:71398
TI Préparation of spirobenzopyran compounds useful in inhibiting biosynthesis and accelerating the excretion of uric acid
IN Harada, Hiroshi; Ohsugi, Eiichi; Yonetani, Yukio; Shinosaki, Toshihiro
PA Shionogi and Co., Ltd., Japan
SO Eur. Pat. Appl., 60 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07D311-22
ICS C07D335-04; C07D221-20; A61K031-35; A61K031-38; A61K031-47
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 415566	A1	19910306	EP 1990-308421	19900731
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 03066669	A2	19910322	JP 1989-203024	19890803
CA 2021926	AA	19910204	CA 1990-2021926	19900725
US 5268386	A	19931207	US 1990-558242	19900726

PRAI JP 1989-203024 19890803
OS MARPAT 115:71398
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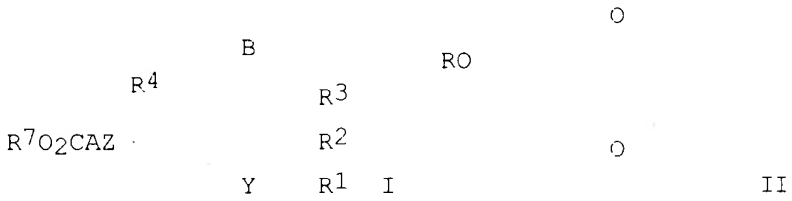

AB The title compds. [I; R1, R2 = H, alkyl, (substituted) Ph, R1R2 = C4-8 carbocyclic; R3 = H, alkyl; R4 = H, halo, NO2, alkyl, (substituted) Ph, etc.; R7 = H, ester residue; A = C1-5 hydrocarbon residue; B = H, O, dithiolane residue; Y = O, S, (substituted) imino; Z = O, (substituted) imino; dotted line indicates single or double bond], useful as antihyperuricemics, are prepd. A mixt. of phenol II (R = H), BrCH2CO2Et, and anhyd. K2CO3 in DMF was stirred at room temp. under N to give 92.5% ether ester II (R = CH2CO2Et), which was sapond. to give 85.6% acid II (R = CH2CO2H). Also prep. were 60 addnl. I, which accelerated the excretion of uric acid at 10 mg/kg in rats, comparable or superior to benzbromarone.
ST spirobenzopyran prepn antihyperuricemic; uric acid excretion spirobenzopyran prepn
IT 69-93-2P, Uric acid, preparation
RL: PREP (Preparation)
(excretion of, spirobenzopyran effects on)
IT 69-93-2, biological studies
RL: BIOL (Biological study)
(metabolic disorders, hyperuricemia, treatment of, spirobenzopyran derivs. for)
IT 2430-55-9P 23121-32-6P 62756-28-9P 62756-43-8P 108838-42-2P
112954-19-5P 135110-57-5P 135110-58-6P 135110-59-7P 135110-60-0P
135110-61-1P 135110-62-2P 135110-63-3P 135110-64-4P 135110-65-5P
135110-66-6P 135110-67-7P **135110-68-8P** 135110-69-9P
135110-70-2P 135110-71-3P 135110-72-4P 135110-73-5P 135110-74-6P
135110-75-7P 135110-76-8P 135110-77-9P 135110-78-0P 135110-79-1P
135110-80-4P 135110-81-5P 135110-82-6P 135110-83-7P 135110-84-8P
135110-85-9P 135110-86-0P 135110-87-1P 135110-88-2P 135110-89-3P
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135111-00-1P 135111-01-2P 135111-02-3P 135111-03-4P 135111-04-5P
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135111-25-0P 135111-26-1P 135111-27-2P 135111-28-3P 135111-29-4P
135111-30-7P 135111-31-8P 135111-32-9P 135111-33-0P 135111-34-1P
135149-45-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of antihyperuricemics)

IT 135111-35-2P 135111-36-3P 135111-37-4P 135111-38-5P 135111-39-6P
135111-40-9P 135111-41-0P 135111-42-1P 135111-43-2P 135111-44-3P
135111-45-4P 135111-46-5P 135111-47-6P 135111-48-7P 135111-49-8P
135111-50-1P 135111-51-2P 135111-52-3P 135111-53-4P 135111-54-5P
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135111-85-2P 135111-86-3P 135111-87-4P 135111-88-5P 135111-89-6P
135111-90-9P 135111-91-0P 135111-92-1P 135149-46-1P 135149-47-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antihyperuricemic agent)

IT 90-24-4 7051-16-3, 3,5-Dimethoxychlorobenzene 14107-97-2,
2,4,6-Trimethoxytoluene 135110-57-5
RL: RCT (Reactant)
(reaction of, in prepn. of antihyperuricemic agent)

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HIGHEST PATENT NUMBER: US6128776
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ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 3 Oct 2000 (20001003/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jul 2000
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jul 2000

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>>> fields. This thesaurus includes catchword terms from the <<<
>>> USPTO/MOC subject headings and subheadings. Thesauri are also <<<
>>> available for the WIPO International Patent Classification <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4, <<<
>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L65 2 L49

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L65 ANSWER 1 OF 2 USPATFULL
AN 97:107277 USPATFULL
TI Process for preparing intermediates for a combinatorial dihydrobenzopyran library
IN Baldwin, John J., Gwynedd Valley, PA, United States
Reader, John C., Princeton, NJ, United States
Dillard, Lawrence W., Hopewell, NJ, United States
Li, Ge, Franklin Park, NJ, United States
Burbaum, Jonathan J., Westfield, NJ, United States
Zeng, Wenguang, Lawrenceville, NJ, United States
PA Pharmacopeia, Inc., Princeton, NJ, United States (U.S. corporation)
PI US 5688997 19971118
AI US 1995-482488 19950607 (8)
RLI Division of Ser. No. US 1995-436120, filed on 8 May 1995 which is a continuation-in-part of Ser. No. US 1994-239302, filed on 6 May 1994, now abandoned
DT Utility
EXNAM Primary Examiner: Raymond, Richard L.
LREP Heslin & Rothenberg, P.C.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Combinatorial libraries are disclosed which are represented by Formula I:

(T'-L).sub.q -S-C(O)-L'-II' I

wherein:

S is a solid support; T'-L- is an identifier residue; and -L'-II' is a ligand/linker residue. These libraries contain dihydrobenzopyrans of the formula: ##STR1## which interact (i.e., as agonists or antagonists) with .alpha. adrenergic receptors, dopamine receptors, .sigma.-opiate receptors, and K.sup.+ channels and are inhibitors of carbonic anhydrase isozymes. They are useful in the treatment of ocular diseases such as glaucoma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **135110-68-8P 174300-53-9P 174300-54-0P**
174300-56-2P 174300-57-3P 174300-58-4P
174300-59-5P 174300-60-8P 174300-61-9P
174300-62-0P 174300-63-1P 174300-64-2P
174300-65-3P 174300-66-4P 174300-67-5P
174300-68-6P 174300-69-7P 174300-70-0P
174300-71-1P 174300-72-2P 174300-73-3P
174300-74-4P 174300-75-5P 174300-76-6P
174300-77-7P
(dihydrobenzopyran pharmaceuticals)

L65 ANSWER 2 OF 2 USPATFULL
AN 93:102798 USPATFULL
TI Certain 3,4-dihydro 4-oxospiro [2H-1 benzopyrans] useful for treating hyperuricemia
IN Harada, Hiroshi, Toyonaka, Japan
Ohsugi, Eiichi, Kawanishi, Japan
Yonetani, Yukio, Nara, Japan
Shinosaki, Toshihiro, Osaka, Japan
PA Shionogi & Co., Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5268386 19931207
AI US 1990-558242 19900726 (7)
PRAI JP 1989-203024 19890803

DT Utility
EXNAM Primary Examiner: Rotman, Alan L.
LREP Wenderoth, Lind & Ponack
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2892
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel heterocyclic compound capable of lowering the uric acid levels in plasma and urine having the formula (I): ##STR1## wherein R.sup.1 and R.sup.2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R.sup.1 and R.sup.2 may form a four- to eight-membered carbon ring together with the carbon atom to which they are attached; R.sup.3 is hydrogen or lower alkyl; R.sup.4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, --OR.sup.5 and --SO.sub.2 NR.sup.6 R.sup.6' ; R.sup.5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxyethyl or ether thereof, or allyl; R.sup.6 and R.sup.6' are independently hydrogen or lower alkyl; R.sup.7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **135110-68-8P**
(prepn. and reaction of, in prepn. of antihyperuricemics)

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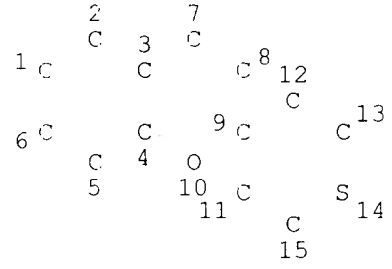

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
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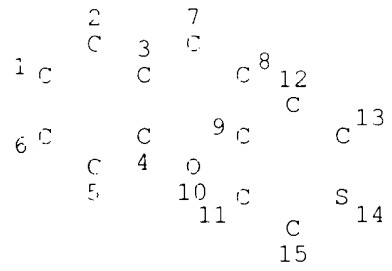

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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L71 3 ANSWERS MARPAT COPYRIGHT 2000 ACS
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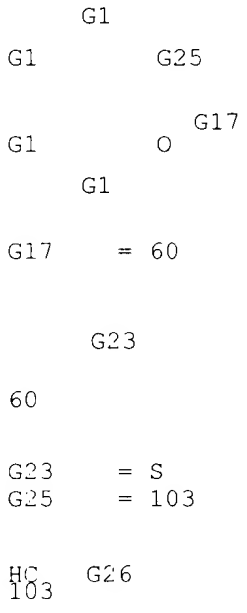
ICS C07D311-04; C07D279-10; C07D275-02; C07D207-00; A61K031-555; A61K031-54; A61K031-50; A61K031-385; A61K031-35
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
TI Combinatorial dihydrobenzopyran library
ST dihydrobenzopyran combinatorial library; adrenergic agonist antagonist
dihydrobenzopyran combinatorial library; dopamine agonist antagonist
dihydrobenzopyran combinatorial library; opiate agonist antagonist
dihydrobenzopyran combinatorial library; carbonic anhydrase inhibitor
dihydrobenzopyran combinatorial library; ocular disease dihydrobenzopyran combinatorial library; glaucoma dihydrobenzopyran combinatorial library
IT Combinatorial library
Eye, disease
Glaucoma (disease)
Polymer-supported reagents
(dihydrobenzopyran pharmaceuticals)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.sigma.-, agonist-antagonist; dihydrobenzopyran pharmaceuticals)
IT Neurotransmitter agonists
Neurotransmitter antagonists

(dopaminergic, dihydrobenzopyran pharmaceuticals)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(opioid, .sigma.-, agonist-antagonist; dihydrobenzopyran pharmaceuticals)
IT Ion channel blockers
Ion channel openers
(potassium, dihydrobenzopyran pharmaceuticals)
IT Adrenergic agonists
Adrenergic antagonists
(.alpha.-, dihydrobenzopyran pharmaceuticals)
IT 135110-68-8P 174300-53-9P 174300-54-0P 174300-55-1P 174300-56-2P
174300-57-3P 174300-58-4P 174300-59-5P 174300-60-8P 174300-61-9P
174300-62-0P 174300-63-1P 174300-64-2P 174300-65-3P 174300-66-4P
174300-67-5P 174300-68-6P 174300-69-7P 174300-70-0P 174300-71-1P
174300-72-2P 174300-73-3P 174300-74-4P 174300-75-5P 174300-76-6P
174300-77-7P 174300-78-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dihydrobenzopyran pharmaceuticals)
IT 89-84-9 107-18-6, 2-Propen-1-ol, reactions 2393-23-9, 4-Methoxybenzylamine 3943-74-6, Methyl vanillate 24424-99-5, Di-tert-butyl dicarbonate 55715-03-2, 3-Nitro-4-(bromomethyl)benzoic acid 82379-38-2, 4-Hydroxymethyl-3-nitrobenzoic acid 96965-31-0 156459-80-2
RL: RCT (Reactant)
(dihydrobenzopyran pharmaceuticals)
IT 65276-91-7P 156459-74-4P 171762-24-6P 174300-80-2P 174300-81-3P
174300-82-4P 174300-83-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(dihydrobenzopyran pharmaceuticals)
IT 89950-93-6P 156459-64-2P 174300-79-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(dihydrobenzopyran pharmaceuticals)
IT 9001-03-0, Carbonic anhydrase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; dihydrobenzopyran pharmaceuticals)

MSTR 2B



DER: ' or pharmaceutically acceptable salts
MEL: ' ' claim 4

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L71 3 ANSWERS MARPAT COPYRIGHT 2000 ACS
IC ICM G01N033-53
ICS G01N033-543; G01N033-551; G01N033-553; G01N033-567; C12Q001-34
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
TI Preparation of benzopyrans as drugs and combinatorial libraries containing them
ST benzopyran prepn drug combinatorial library; carbonic anhydrase inhibitor benzopyran prepn
IT Combinatorial library
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 9001-03-0, Carbonic anhydrase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibitors; prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 135110-68-8P 174300-53-9P 174300-56-2P 174300-57-3P 174300-58-4P
174300-59-5P 174300-60-8P 174300-61-9P 174300-62-0P 174300-63-1P
174300-64-2P 174300-65-3P 174300-66-4P 174300-67-5P 174300-68-6P
174300-70-0P 174300-71-1P 174300-72-2P 174300-73-3P 174300-74-4P
174300-75-5P 174300-76-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 89-84-9 107-18-6, Allyl alcohol, reactions 2393-23-9, 4-Methoxybenzylamine 3943-74-6, Methyl vanillate 24424-99-5, Di-tert-butyl dicarbonate 55715-03-2, 3-Nitro-4-bromomethylbenzoic acid 82379-38-2, 4-Hydroxymethyl-3-nitrobenzoic acid 96965-31-0, tert-Butyl 4-acetoxymethyl-3-nitrobenzoate 156459-80-2, 9-Pentachlorophenoxy-1-nonanol
RL: RCT (Reactant)
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)
IT 65276-91-7P 89950-93-6P 156459-64-2P 156459-74-4P 171762-24-6P
174300-79-9P 174300-81-3P 174300-82-4DP, resin-bound 174300-82-4P
190602-46-1DP, resin-bound 190602-47-2DP, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of benzopyrans as drugs and combinatorial libraries contg. them)

MSTR 1B

G17 = 54

G20

54

G20 = S
G25 = 103

HC G26
103

DER: or pharmaceutically acceptable salts
MPL: claim 4
NTE: substitution is restricted

L71 3 ANSWERS MARPAT COPYRIGHT 2000 ACS
IC ICM G01N033-543
ICS C07C233-11
NCL 436518000
CC 27-14 (Heterocyclic Compounds (One Hetero Atom))
TI Preparation of dihydrobenzopyran combinatorial libraries
ST dihydrobenzopyran combinatorial library prepn
IT Combinatorial library
(prepn. of dihydrobenzopyran combinatorial libraries)
IT 65276-91-7P 89950-93-6P 96965-31-0P 171762-24-6P 174300-81-3P
174300-82-4P 214203-19-7P 214203-20-0P 214203-21-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of dihydrobenzopyran combinatorial libraries)
IT 89-84-9 2393-23-9, 4-Methoxybenzylamine 3943-74-6, Methyl vanillate 55715-03-2, 4-Bromomethyl-3-nitrobenzoic acid 82379-38-2, 4-Hydroxymethyl-3-nitrobenzoic acid 156459-80-2, 9-Pentachlorophenoxy-1-nonanol
RL: RCT (Reactant)
(prepn. of dihydrobenzopyran combinatorial libraries)

MSTR 4B

G1

G1 G25

G17
G1 O

G1

G17 = 54

G20

54

G20 = S
G25 = 103

HC G26
103

DER: or pharmaceutically acceptable salts
MPL: disclosure
NTE: substitution is restricted

ALL ANSWERS HAVE BEEN SCANNED

=> d bib abs tot

L71 ANSWER 1 OF 3 MARPAT COPYRIGHT 2000 ACS
AN 129:290059 MARPAT
TI Preparation of dihydrobenzopyran combinatorial libraries
IN Baldwin, John J.; Reader, John C.; Dillard, Lawrence W.; Li, Ge; Zeng, Wenguang
PA Pharmacopeia, Inc., USA
SO U.S., 67 pp. Cont.-in-part of U.S. Ser. No. 436,120, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5821130	A	19981013	US 1995-552698	19951103
	US 5688997	A	19971118	US 1995-482488	19950607
	US 6017768	A	20000125	US 1996-733803	19961018
	WO 9716729	A1	19970509	WO 1996-US17982	19961104
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9676750	A1	19970522	AU 1996-76750	19961104
	EP 864087	A1	19980916	EP 1996-939617	19961104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1994-239302 19940506
US 1995-436120 19950508
US 1995-552698 19951103
US 1996-733803 19961018
WO 1996-US17982 19961104

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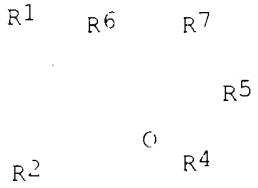


AB Prepn. of title libraries comprising dihydrobenzopyran drugs I [R1 = OH, OCH2CO2H, alkylcarbamoylalkoxy, etc.; R2 = H or alkyl; R4,R5 = H or (un)substituted alkyl; R4R5 = (heteroatom-interrupted) alkylene, etc.; 1 of R6,R7 = H and the other = OH or (un)substituted amino; R6R7 = O, OCH2CH2S, etc.](no data) was described. I are attached to solid supports with linkers via functional groups R1.

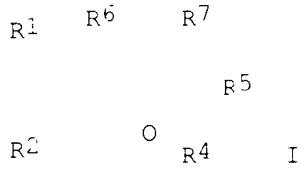
L71 ANSWER 2 OF 3 MARPAT COPYRIGHT 2000 ACS

AN 127:17591 MARPAT
TI Preparation of benzopyrans as drugs and combinatorial libraries containing them
IN Baldwin, John J.; Dillard, Lawrence W.; Li, Ge; Reader, John C.; Zeng, Wenguang
PA Pharmacopeia, Inc., USA
SO PCT Int. Appl., 165 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9716729	A1	19970509	WO 1996-US17982	19961104
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5821130	A	19981013	US 1995-552698	19951103
AU 9676750	A1	19970522	AU 1996-76750	19961104
EP 864087	A1	19980916	EP 1996-939617	19961104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1995-552698 19951103
US 1994-239302 19940506
US 1995-436120 19950508
US 1996-733803 19961018
WO 1996-US17982 19961104

GI



AB Title benzopyrans (I; R1 = OH, OCH2OH, OCH2CO2H, etc.; R2 = H or alkyl; R4,R5 = H, alkyl, piperazinoalkyl, etc.; R4R5 = alkylene, CH2CH2OCH2CH2, CH2CH2NR8CH2CH2, etc.; 1 of R6,R7 = H and the other = H, OH, alkylamino, etc.; R6R7 = O, SCH2CH2S, OCH2CH2O, etc.; R8 = H, alkoxycarbonyl, alkylcarbamoyl, alkanoyl, etc.) were claimed as carbonic anhydrase inhibitors (no data) and as components of bead-linked combinatorial libraries.

L71 ANSWER 3 OF 3 MARPAT COPYRIGHT 2000 ACS
AN 124:202020 MARPAT
TI Combinatorial dihydrobenzopyran library
IN Baldwin, John J.; Reader, John C.; Dillard, Lawrence W.; Burbaum, Jonathan J.; Zeng, Wenguang; Li, Ge
PA Pharmacopeia, Inc., USA
SO PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9530642	A1	19951116	WO 1995-US5940	19950508
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB,				

GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW,
NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

CA	2189634	AA	19951116	CA 1995-2189634	19950508
AU	9525869	A1	19951129	AU 1995-25869	19950508
AU	691296	B2	19980514		
EP	758313	A1	19970219	EP 1995-920411	19950508
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP	10500112	T2	19980106	JP 1995-529207	19950508
PRAI US	1994-239302	19940506			
WO	1995-US5940	19950508			

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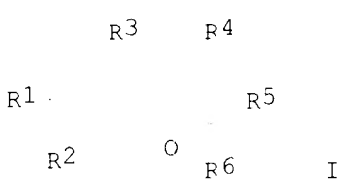
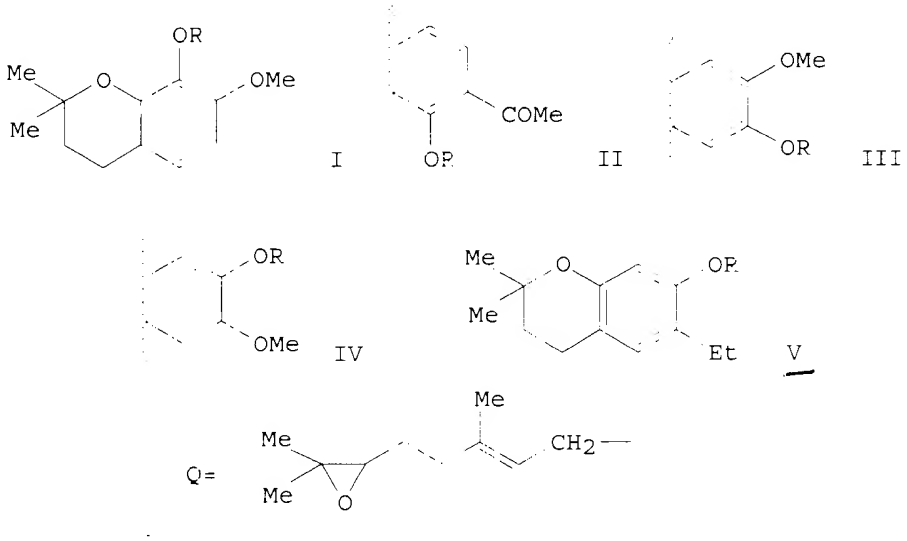


AB Combinatorial libraries, represented by divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene-supported reagents, contain dihydrobenzopyrans I [R1 = OH, OCH2CO2H, CO2H, etc.; R2 = H, alkyl; R3 = R4 = H, R3 = H, R4 = OH, R3R4 = -SCH2CH2S-, etc.; R5, R6 = H, (substituted) alkyl, aryl, etc.] which interact (i.e., as agonists or antagonists) with .alpha. adrenergic receptors, dopamine receptor, .sigma.-opiate receptors, and K+ channels and are inhibitors of carbonic anhydrase isoenzymes. They are useful in the treatment of ocular diseases such as glaucoma. Compds. I are effective at 0.1-1.0 mg/kg per day in humans.

AN 1982:598389 CAPLUS
DN 97:198389
TI Insect antijuvenile hormone analogs. II. Synthesis of terpenoxychromene derivatives
AU Gan, Lixian; Wu, Biqi
CS Shanghai Inst. Org. Chem., Acad. Sin., Shanghai, Peop. Rep. China
SO Huaxue Xuebao (1981), 39(7-8-9), 777-92
CODEN: HHHPA4; ISSN: 0567-7351
DT Journal
LA Chinese
CC 30-10 (Terpenes and Terpenoids)
Section cross-reference(s): 5
GI

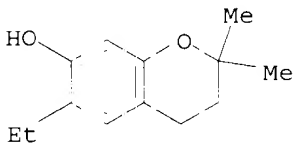


AB Twenty-five terpenoxychromene derivs. I-V [R = geranyl, (E)-MeOCMe2(CH2)3CMe:CHCH2, (E)-EtOCMe2(CH2)3CMe:CHCH2, Q] were prepd. as potential juvenile hormone analogs by alkali-catalyzed condensation of I-V (R = H) with terpenoid halides.
ST juvenile hormone terpenoxychromene prepn
IT Condensation reaction
(of hydroxychromenes with terpenyl halides in prepn. of juvenile hormones)
IT Juvenile hormones
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of terpenoxychromene derivs. as potential)
IT 5389-87-7 42273-13-2 43119-82-0 83565-06-4
RL: RCT (Reactant); PACT (Reactant or reagent)
(condensation of, with hydroxychromenes)
IT 24672-84-2 74094-51-2 76970-49-5 83565-05-3
RL: RCT (Reactant); PACT (Reactant or reagent)
(condensation of, with terpenyl halides)
IT 83565-04-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
IT 69309-22-4P 74094-44-3P 74094-45-4P 83564-83-4P 83564-84-5P 83564-85-6P 83564-86-7P

83564-87-8P 83564-88-9P 83564-89-0P 83564-90-3P 83564-91-4P
83564-92-5P 83564-93-6P
83564-94-7P 83564-95-8P 83564-96-9P 83564-97-0P 83564-98-1P
83564-99-2P 83565-00-8P
83565-01-9P 83565-02-0P 83565-03-1P **83574-52-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as potential juvenile hormone analog)

IT **83574-52-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as potential juvenile hormone analog)

RN 83574-52-1 CAPLUS
CN 2H-1-Benzopyran-7-ol, 6-ethyl-3,4-dihydro-2,2-dimethyl- (9CI) (CA INDEX NAME)



=> d 16 std bib ab hit

L13 ANSWER 16 OF 16 USPATFULL
AN 93:14593 USPATFULL
TI Treatment of **cocaine addiction**
IN Blum, Kenneth, San Antonio, TX, United States
Trachtenberg, Michael C., Houston, TX, United States
PA Matrix Technologies, Inc., Houston, TX, United States (U.S. corporation)
PI US 5189064 19930223
AI US 1990-523390 19900514 (7)
RLI Continuation of Ser. No. US 1987-105353, filed on 7 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 1985-757733, filed on 22 Jul 1985, now patented, Pat. No. US 4761429
DT Utility
LN.CNT 1363
INCL INCLM: 514/561.000
INCLS: 514/810.000; 514/811.000; 514/812.000
NCL NCLM: 514/561.000
NCLS: 514/810.000; 514/811.000; 514/812.000
IC [5]
ICM: A61K031-195
EXF 514/561; 514/810; 514/811; 514/812
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 93:14593 USPATFULL
TI Treatment of **cocaine addiction**
IN Blum, Kenneth, San Antonio, TX, United States
Trachtenberg, Michael C., Houston, TX, United States
PA Matrix Technologies, Inc., Houston, TX, United States (U.S. corporation)
PI US 5189064 19930223
AI US 1990-523390 19900514 (7)
RLI Continuation of Ser. No. US 1987-105353, filed on 7 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 1985-757733, filed on 22 Jul 1985, now patented, Pat. No. US 4761429
DT Utility
EXNAM Primary Examiner: Friedman, S. J.
LREP Cooper, Iver P.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1363
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Cocaine addiction** is treated by administration of an endorphinase or enkephalinase inhibitor, and optionally, a dopamine precursor, or a serotonin precursor, a GABA precursor, or an endorphin or enkephalin releaser. These components promote restoration of normal neurotransmitter function and are non-**addictive**. Use of the dopamine precursors L-phenylalanine or L-tyrosine, the enkephalinase inhibitor D-phenylalanine and/or the serotonin precursor L-tryptophan is especially preferred.
TI Treatment of **cocaine addiction**
AB **Cocaine addiction** is treated by administration of an endorphinase or enkephalinase inhibitor, and optionally, a dopamine precursor, or a serotonin precursor, a GABA precursor, or an endorphin or enkephalin releaser. These components promote restoration of normal neurotransmitter function and are non-**addictive**. Use of the dopamine precursors L-phenylalanine or L-tyrosine, the enkephalinase inhibitor D-phenylalanine and/or the serotonin precursor L-tryptophan is especially preferred.
SUMM This invention relates to the use of enkephalinase or endorphinase

inhibitors, and, optionally, dopamine precursors, serotonin precursors and/or GABA precursors, in the treatment of **cocaine addiction**.

SUMM1 **Cocaine** is a naturally occurring stimulant derived from the leaves of the coca plant, Erythroxylon coca. In 1864, **cocaine** was isolated from the coca leaves.

SUMM1 Coca leaves contain only about one-half of one percent pure **cocaine** alkaloid. When chewed, only relatively modest amounts of **cocaine** are liberated, and gastrointestinal absorption is slow. Certainly, this explains why the practice of chewing coca leaves has never been a public health problem in Latin America. The situation changes sharply with the abuse of the alkaloid itself.

SUMM1 The **cocaine** user experiences three stages of drug effects. The first, acute intoxication ("binge"), is euphoric, marked by decreased anxiety, enhanced self-confidence and sexual appetite, and may be marred by sexual indiscretions, irresponsible spending, and accidents attributable to reckless behavior. The second stage, the ("crash"), replaces euphoria by anxiety, fatigue, irritability and depression. Some users have committed suicide during this period. Finally, the third stage, "anhedonia," is a time of limited ability to derive pleasure from normal activities and of craving for the euphoric effects of **cocaine**. See Gawin and Kleber, Medical Management of **Cocaine** Withdrawal, 6-8 (APT Foundation).

SUMM1 In the past, physicians tended to treat primarily the acute symptoms of **cocaine** abuse, prescribing drugs such as propranolol to treat erratic heart rhythms, diazepam to control convulsions and chlorpromazine to relieve psychosis (paranoia). However, these treatment approaches do not relieve the patient's craving for **cocaine**.

SUMM1 A number of drugs have been suggested for use in weaning **cocaine** users from their dependency. Antidepressants, such as lithium and desipramine, were studied by Tennant and Rawson, in PROBLEMS OF DRUG DEPENDENCE 1982, 351-55 (NIDA Res. Monogr. Ser. 43, 1983); Gawin, Psychosomatics, 27: 24-29 (1986); Gawin and Kleber, Arch. Gen. Psychiatry, 41: 903-9 (1984); Kleber and Gawin, J. Clin. Psychiatry 45 (12, Sec. 2): 18-23 (1984).

SUMM1 Certain therapeutic agents are favored by the "dopamine depletion hypothesis." It is well established that **cocaine** blocks dopamine re-uptake, acutely increasing synaptic dopamine concentrations. However, in the presence of **cocaine**, synaptic dopamine is metabolized as 3-methoxytyramine and excreted. The synaptic loss of dopamine places demands on the body for increased dopamine synthesis, as evidenced by the increase in tyrosine hydroxylase activity after **cocaine** administration. When the precursor supplies are exhausted, a dopamine deficiency develops. See Dackis and Gold, Neurosci. Biobehav. Rev., 9:469-77 (1985); Gold and Dackis, Clin. Therapeutics, 7:6-21 (1984). This hypothesis led to the testing of bromocriptine, a dopamine receptor agonist. Dackis, et al., Int. J. Psychiat. Med., 15: 125-135 (1985); Tennant and Sagherian, Arch. Intern. Med., 147:109 (1987). A second approach was the administration of Amantadine, a dopamine releaser. Another approach, also based on this hypothesis, was to provide a precursor for dopamine, such as L-dopa, See Rosen et al., Am. J. Psychiat., 143:1493 (Nov. 1986), or L-tyrosine, Gold, et al., Soc. Neurosci. Abstr., 9:157 (1983); Rosecan, Abstract, VII World Congress of Psychiatry, Vienna, Austria (1983);

SUMM Verebey and Gold, in PSYCHOPHARMACOLOGY: IMPACT ON CLINICAL PSYCHIATRY 219-41 (Morgan, ed., 1985) (1985), describe a regimen for the treatment of **cocaine addiction** that contemplates administration of L-tyrosine, L-tryptophan, thiamine, riboflavin, niacin, pantothenic acid, pyridoxamine, ascorbic acid, folic acid and cyanocobalamin. Their composition does not include any enkephalinase or endorphinase inhibitor or any enkephalin or endorphin releaser. Nor does it include any GABA precursor.

SUMM D-phenylalanine is an inhibitor of enzymes involved in the metabolism of endorphins and enkephalins. Ehrenpreis, Subs Alc Act/Mis, 3: 231-239 (1982). It has anti-alcohol craving activity, see copending U.S. application Ser. No. 06/757,733 and counterpart PCT Publ WO 86/01405, and has been studied as a potential anti-depressive, Heller, U.S. Pat. No. 4,179,044; Heller in Modern Pharmacology 397 (Mosnaim and Wolf, 1979); and analgesic agent, see Ehrenpreis, U.S. Pat No. 4,439,452. There have been no reports of its use in the treatment of **cocaine addiction**.

SUMM The obsessive drug-seeking behavior demonstrated by **cocaine addictt** seems to be due to the drug's overwhelming influences on the "reward center" in the brain.. In this regard, **cocaine** is believed to cause an intense stimulation of the reward center, through a "concert" of neurotransmitter events allowing the mood-altering neurotransmitter dopamine to remain active longer than normal. It is this enhanced stimulation, perceived as euphoria, that is repeatedlV sought by **cocaine** abusers. Our invention breaks the biological hold of **cocaine** on its victims by pharmacological manipulation of neurotransmitters operating at botlpatecholamine and opioid receptors.

SUMM It has now been found that by restoring the function of the neurotransmitter systems implicated in the acute and chronic pharmacological effects of **cocaine**, the psychological dependence of the patient on **cocaine** is diminished. It is expected that this treatment will therefore reduce recidivism.

SUMM One of **cocaine**'s principal acute effects is the blocking of re-uptake of dopamine, resulting in increased dopamine levels, and dopaminergic transmission and therefore in the euphoria characteristic of the drug. However, chronic use of **cocaine** leads to dopamine depletion.

SUMM This problem, which is the root of the dependence established by **cocaine**, may be tackled in several ways. In the most general embodiment of this invention, the opioidergic system is used to modulate the dopaminergic system. More specifically, our therapeutic approach is to elevate the levels of the opioid peptides (endorphins and enkephalins) that regulate dopamine synthesis and release.

SUMM It is inadvisable however, merely to administer the desired opioid peptides. They are easily degraded in the digestive tract, and are very **addictive**. Both disadvantages discourage their clinical use.

SUMM In another preferred embodiment, a dopamine precursor, such as L-tyrosine or L-phenylalanine, is also administered. If there is a deficit of dopamine, as would be expected in a chronic **cocaine** user, the body would convert the dopamine precursor directly or indirectly to dopamine, thereby restoring dopamine levels to normal and

reducing the feeling of dysphoria inadequate stimulation of the "reward" centers attributable to depressed dopamine levels) which invites readministration of the drug.

SUMM In another preferred embodiment, a serotonin precursor, such as L-tryptophan, is also provided. Reduction of serotonergic transmission results in a decrease in the utilization of hypothalamic enkephalin. See Schwartz and Mocchetti, Proc. II World Congr. Biol. Psych., 1986. It is expected that this will in turn depress the dopaminergic system. See Devan, et al., J. Neurochem., 49:665-70 (1987). In the short term, **cocaine** activates the serotonergic receptors through release of neuronal serotonin. Chronic use of **cocaine**, however, results in down regulation of CNS serotonin and thus, indirectly, in reduced dopaminergic activity. The serotonin precursor may be used with or without the aforementioned dopamine precursor.

SUMM In another preferred embodiment, a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), e.g., L-glutamic acid, is also given. To date there is no evidence that cocaine per se affects GABAergic activity (i.e., storage, release, or turnover), however, a novel approach to chronic **cocaine** toxicity may involve the GABAergic pathway.

SUMM Repeated **cocaine** use has been linked to a sensitization of the brain resulting in convulsions. Post, et al., in **COCAINE**: CLINICAL AND BIOBEHAVORIAL ASPECTS, 107-165, Uhlenhuth, et al., eds., 1987). It has been found that giving an experimental animal a small dose of **cocaine** once a day sensitizes its brain to **cocaine** and progressively lowers the threshold for seizures. After several days of such administration, a small, previously non-convulsive, dose of **cocaine** produces a convulsive seizure; moreover a high percentage of these seizures result in the death of the experimental animal. This phenomenon is not due to any accumulation of the drug or its metabolites in the body; it represents a true sensitization of the brain to the effects of **cocaine**. With continued treatment, surviving animals may develop seizures spontaneously--in the absence of **cocaine**. There seems to be a permanent lowered seizure threshold in the organism, analogous to "kindling," the sensitization to convulsive seizures induced by repeated, small electrical stimulation of the brain. **Cocaine** induced kindling could explain seizures or death in individuals who repeatedly use small amounts of the drug. It implies that each time an individual uses **cocaine**, there is a small, but progressive increase in sensitivity of the brain to it. Thus, repeated use of **cocaine** without experiencing a seizure is no guarantee for continued safety.

SUMM GABA as well as GABA agonists, injected intracerebroventricularly, will reduce seizure activity during alcohol withdrawal in rodents. Pozdyeyev, V.M. NEUROTRANSMITTER PROCESSES AND EPILEPSY 112 (1983). Also amino oxyacetic acid, ethanolamine-o-sulfate and sodium valproate, which increase GABA content, suppress alcohol withdrawal signs in rodents. Utilization of L-glutamine as a natural way to affect brain GABA levels should significantly reduce the chance of seizure activity in the chronic **cocaine** abuser.

SUMM **Cocaine addicts** often exhibit various nutritional deficiencies. Consequently, it is preferable to further provide certain vitamins and minerals, particularly pantothenic acid (B5), pyridoxal phosphate (B6), magnesium, calcium, and zinc. Note that vitamin B6 is important as a co-factor in the synthesis of dopamine, serotonin and

GABA.

SUMM Thus, an endorphinase or enkephalinase inhibitor may be combined with one or more of (a) a dopamine precursor (b) a serotonin precursor, (c) a GABA precursor, (d) an endorphin or enkephalin releaser or (e) replacement vitamins and minerals in order to restore the former **cocaine** user's neurotransmitter systems (and general health and well being) to normal. In an especially preferred embodiment, all of the foregoing elements are administered to the patient.

SUMM The major goals in the treatment of long-term recovery from **cocaine** abuse should include:

SUMM 6). reduced **cocaine**-induced sensitization to convulsive seizures.

SUMM It has been reported that there is a 400:1 greater risk for **cocaine** dependence in these patients with a familiar history of alcoholism. Since we have found, as described in our copending application Ser. No. 08/757,733, that endorphinase and enkephalinase inhibitors are useful in the treatment of ethanol abuse, we believe that the compositions of this invention are of particular value in the treatment of patients suffering from both **cocaine** **addiction** and alcoholism.

DETD We believe that the substrate for **cocaine** reward is mediated by regions in the brain, "pleasure centers" or "reward centers," which are high in dopamine. These regions include the dopamine-containing nucleus accumbens, and its projection to limbic structures and frontal cortex. In this regard, it has been observed that if dopamine projections to limbic and cortical areas are lesioned the self-administration of **cocaine** by animals is greatly reduced. Selective dopamine receptor antagonists, like haloperidol, attenuate or block **cocaine** self-administration in animals. Similarly, in humans, pretreatment with dopamine receptor antagonists will block stimulant-induced "euphoria". Additionally, dopamine receptor agonists (eg. apomorphine, Piribedil) have rewarding actions. These and other studies suggest that **cocaine** reward is mediated via activation of dopamine brain circuits.

DETD **Cocaine** effects on dopamine containing neurons are such that the acute effects involve dopamine activation while the chronic effects induce dopamine deficit. For example, acute use of cocaine activates dopamine circuits by blocking synaptic re-uptake of dopamine, resulting in increased postsynaptic receptor stimulation as these sites are flooded with dopamine. This action of **cocaine** is important since it eliminates a major means by which dopamine is conserved and recycled. Norepinephrine, a dopamine metabolite and a reward neurotransmitter in its own right, is also activated.

DETD However, during chronic abuse of **cocaine**, a shunt is established whereby the net effect leads to a dopamine depletion state. Increased levels of the synaptic dopamine metabolite, 3-methoxytyramine, are found after **cocaine** administration in animals; receptor affinity changes and brain dopamine levels are decreased after repeated **cocaine** administration in animals. Similarly, with chronic **cocaine** use, catecholamines including norepinephrine are depleted and inhibited.

DETD In effect the action of **cocaine** is as follows: (1) acute blockade of dopamine re-uptake; (2) acute increase in synaptic dopamine; (3) acute increase in dopamine neurotransmission; (4) chronic increase in postsynaptic dopamine receptor number; (5) increased levels of

synaptic dopamine metabolites; (6) decreased brain dopamine metabolites; (7) inhibition of dopamine vesicle binding; (8) increased tyrosine hydroxylase activity.

DETD The stability of the NE-ATP-protein- ion storage complex can be disrupted by some compounds which act as chelators of Mg++. This may be linked to the magnesium deficiency sometimes found in chronic **cocaine** abusers. In this regard, chronic administration of **cocaine** produces an increase in NE turnover.

DETD Uptake I is energy dependent, requiring ATP which is broken down by a sodium dependent ATPase. This is a high-affinity process, which means that it is efficient at the eliminating low concentrations of NE from the synaptic cleft. The neuronal uptake system transports NE into the nerve terminal. Inside the nerve terminal most of the NE is taken up into storage vesicles. Inhibitors of this process include: **cocaine**, tricyclic anti-depressants, amphetamine and tyramine.

DETD High intraneuronal amounts of DA inhibits tyrosine hydroxylase by end-product inhibition, thus decreasing the rate of DA synthesis. Furthermore, the rate-limiting step in the synthesis of DA is the conversion of tyrosine to L-dopa by tyrosine hydroxylase. Under normal situations tyrosine hydroxylase is completely saturated with L-tyrosine and thus increase in circulatory tyrosine levels do not increase the rate of DA synthesis. However, this fact changes when there is a deficit in both the amount of DA and when tyrosine hydroxylase is compromised as under the influence of **cocaine**.

DETD Dopamine is stored in storage granules where the catecholamine is complexed with chromogranins, divalent metal ions and ATP. DA is believed to be released into the synaptic cleft by exocytosis. As with NE, this is a calcium dependent process and occurs in response to action potentials reaching nerve terminals or to drugs. The following substances can increase DA release; **cocaine**, (+)-amphetamine, methylamphetamine, tyramine, amantadine, m-phenmetrazine, phentermine and nomifensine. In addition to causing the release of DA, these compounds can also, to different degrees, inhibit neuronal re-uptake of DA.

DETD **Cocaine**, by virtue of blocking re-uptake of DA into presynaptic nerve terminals, prolongs the effect of release DA in the synaptic cleft.

DETD L-Phenylalanine is an essential amino acid which is also a precursor for the synthesis of the neurotransmitters dopamine and norepinephrine. These neurotransmitters, as measured by their metabolites, HVA, DOPAC, and MHPH, are significantly altered during periods of intense exercise and physical endurance. L-phenylalanine may be used instead or in combination with L-tyrosine or L-dopa to restore dopamine reserves after depletion by **cocaine** abuse.

DETD **Cocaine** also affects opiodergic action. With chronic exposure **cocaine** to rats, dose-dependent alteration of naloxone binding was observed. Opiate receptor density was significantly decreased in several brain structures, while it was increased in the lateral hypothalamus. It appears that opiate binding was specifically affected in "reward centers" and not in other regions. P. Hammer, Jr., et al., Abst., Neuroscience Abstracts, 13 (2): 85 No. 2710 (Apr. 1987). Furthermore, naloxone, in another study, effectively blocked the threshold lowering action of **cocaine** in reward centers of the brain. Bain and Korwetsky, Life Sci 40: 1119-1125 (1987).

DETD Moreover, **cocaine** appears to affect the analgesic action of certain opiates. (Misra, A. L. Pontani, R. G. and Vadlamani, pain 28(1): 129-38, 1987).

DETD We believe that the reinforcing action of **cocaine** may be mediated in part by opiate systems in brain reward centers, which are altered by chronic **cocaine** exposure.

DETD It is unknown at the present time whether these agents, which are candidate E5 agonists, have potential **addiction** liability, tolerance and other toxicological problems associated with their clinical use. The probable **addictive** nature of many of these modified, enzyme resistant surrogates would significantly reduce their clinical application.

DETD Thus, an enkephalin releaser may be combined with an enkephalinase inhibitor to achieve a high degree of enkephalinergic activity at the synapse to further augment the release of neuronal dopamine. This will act as a form of "replacement therapy" and reduce "craving" for **cocaine**. This treatment will be most useful during the 1-2 months following **cocaine** detoxification.

DETD Chronic use of **cocaine** reduces concentrations of serotonin and its metabolite. **Cocaine** apparently reduces uptake of the serotonin precursor tryptophan, thereby reducing serotonin synthesis. **Cocaine** also reduces tryptophan hydroxylase activity. Thus, **cocaine** decreases serotonergic action. Reith, et al., Brain Res. 342(1): 145-8 (1985).

DETD Unlike tyrosine hydroxylase, under normal physiological conditions, tryptophan hydroxylase is not saturated, i.e., the enzyme is not working to full capacity and thus tryptophan hydroxylase activity is significantly affected by L-tryptophan. The amount of available free L-tryptophan is dependent on a number of factors including the concentration of circulating L-tryptophan in the plasma at the rate of its uptake in the brain and presynaptic terminals. We contemplate using L-tryptophan to restore the serotonergic system disrupted by **cocaine**.

DETD Serotonin can be released into the synaptic cleft by the process of exocytosis in response to action potentials and to drugs. Facilitation of 5HT release can be accomplished with **cocaine**, (+)-amphetamine, methamphetamine, fenfluramine, parachloramphetamine, clorimipramine (clomipramine) and amitriptyline.

DETD Three types of 5HT receptors (5HT-1, -2 and -3) have been proposed. 5HT receptor agonists include LSD, quipazine, N,N-dimethyl-tryptamine (DMT). 5HT receptor antagonists include cyproheptadine, methysergide, LSD, 2 bromo-LSD (BOL), ketanserin, xylamidine, cinanserin and l-(-)-**cocaine**.

DETD Inhibitors of neuronal uptake of 5HT include the tricyclic anti-depressants imipramine, desimipramine, amitriptyline, chlorimipramine, fluvoxamine; fenfluramine [an anorectic agent] and **cocaine**. Any 5HT not bound in storage will be converted into metabolites by MAO. However, if MAO is inhibited, serotonin is metabolized to N-Methyl, or N-N-dimethyl by O-methyl-transferase (COMT).

DETD GABA, taken back into the presynaptic neuron after release and receptor interaction, is recycled as a potentially reuseable transmitter. GABA is enzymatically metabolized in both the nerve terminal and glial tissue and converted, in the presence of A-oxoglutamic acid, to succini semialdehyde by the mitochondrial enzyme GABA aminotransferase (GABA-T). The succinic acid which is formed enters the tricarboxylic acid (Krebs) cycle. GABA-T requires pyridoxal phosphate as a co-factor. Succinic semialdehyde is rapidly oxidized to succinic acid by the enzyme succinic semialdehyde dehydrogenase which also involves NAD and NADH as co-factors. Our formulation for **cocaine** takes this fact into account by adding pyridoxal-5-phosphate as a promoter of the oxidative-reductive pathway.

DETD In this regard, GABA concentrations can be increased by the administration, to animals, of the following inhibitors of GABA-T: ethanolamine-O-sulphate, gamma acetylenic GABA, **gamma vinyl GABA**, gabaculline, hydrazinopripionic acid, sodium di-N-propylacetate (sodium valproate) and aminooxyacetic acid

(inhibitor of Vitamin B6) (Bloom. FE, In: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 247-248, (Goodman, et al., eds., 1985).

DETD No reports to date have suggested that precursors of GABA are useful in the treatment of **cocaine** abuse. We believe that since the GABA system inhibits the release of dopamine, a GABA precursor may reduce the severity of the dopamine depletion associated with **cocaine**. In addition, as mentioned earlier, we believe it can reduce seizure propensity.

DETD An example of an amino acid formulation for treating **cocaine addiction** is as follows:

DETD Similar to its use in **cocaine** abusers, ascorbic acid (vitamin C) affects the opioid receptor system and reduces opiate- and alcohol withdrawal reactions as well as its combination with DL Phenylalanine in a number of patients, has resulted in reduced alcohol craving.

DETD The formulation of Example 1 was administered to 26 **cocaine** dependent subjects under treatment for **cocaine addiction**. One month after release, only three had reverted to using **cocaine**. Within five days, experimental patients exhibited (as compared to control patients) a decided decrease in agitation, outside focus and most importantly drug hunger. There was much less acting out and less craving. The vital signs were more stable with a reduction in sympathetic discharge, i.e., the severity of the **cocaine** "crash" was reduced. Normally, viewing street corners associated with drug traffic and drug dealers' houses, produces agitation in patients. With our treatment this was greatly reduced. The patients were also more cooperative.

DETD It may also be desirable to modulate cholinergic transmission with appropriate agonists, antagonists, precursors, releasers, or degradation inhibitors. There is some evidence that **cocaine** causes non-competitive inhibition of the cholinergic system. See Karpen, et al., PNAS (USA), 79: 2539-13 (1982); Karpen, et al., Biochemistry, 25: 1777-81 (1986).

CLM What is claimed is:

1. A method for treating **cocaine addiction** which comprises administering to a subject an opiate destruction-inhibiting amount of at least one substance which inhibits the enzymatic destruction of neuropeptidyl opiates, said substance being selected from the group consisting of: (i) hydrocinnamic acid, (ii) D-form mono amino acids, (iii) thiolbenzyl amino acids, (iv) di- and tripeptides of essential amino acids in D-form (v) enkephalin fragments, (vi) oligopeptides or polypeptides comprising the dipeptides D-Phe D-Leu or D-Phe.D-Met and (k) a neurotransmitter synthesis-promoting amount of at least one neurotransmitter precursor selected from the group consisting of the dopamine precursors L-Phe, L-dopa and L-Tyr, the serotonin precursors 5-hydroxytryptophan and L-Trp, and the GABA precursors, L-Gln, L-glutamic acid and L-glutamate, the amount of said substance and said neurotransmitter precursor being chosen so that said composition is effective in reducing the subject's craving for **cocaine**.

2. A method for treating **cocaine addiction** which comprises administering to a subject an opiate destruction-inhibiting amount of at least one substance which inhibits the enzymatic destruction of neuropeptidyl opiates, said substance being selected from the group consisting of: (i) amino acids, (ii) peptides, and (iii) analogues or derivatives of (i) or (ii) above, and (k) a neurotransmitter synthesis-promoting amount of at least one neurotransmitter precursor selected from the group consisting of the dopamine precursors L-Phe, D-dopa and L-Tyr, the serotonin precursors 5-hydroxytryptophan and L-Trp, and the GABA precursors, L-Gln, L-glutamic acid and L-glutamate, the amount of said substance and said

neurotransmitter precursor being chosen so that said composition is effective in reducing the subject's craving for **cocaine**.

10. A pharmaceutical composition for the treatment of **cocaine addiction** which consists essentially of (a) an opiate destruction-inhibiting amount of at least one substance which inhibits the enzymatic destruction of a neuropeptidyl opiate, said substance being selected from the group consisting of (i) amino acids, (ii) peptides, and (iii) analogues or derivatives of (i) or (ii) above, and (b) a neurotransmitter synthesis-promoting amount of at least one neurotransmitter precursor selected from the group consisting of the dopamine precursors L-Tyr, L-Phe and L-dopa, the serotonin precursors L-Trp and 5-hydroxytryptophan, and the gamma amino butyric acid (GABA) precursors L-glutamine, L-glutamic acid and L-glutamate, the amount of said substance and said neurotransmitter precursor being chosen so that the composition is effective in reducing the subject's craving for **cocaine**.

=> d 12 bib ab hit

L16 ANSWER 12 OF 16 MEDLINE DUPLICATE 9
AN 1998039808 MEDLINE
DN 98039808
TI **Gamma-vinyl GABA** attenuates **cocaine**
-induced lowering of brain stimulation reward thresholds.
AU Kushner S A; Dewey S L; Kornetsky C
CS Department of Pharmacology, Boston University School of Medicine, MA 02118, USA.
NC DA02816 (NIDA)
K05-DA00093 (NIDA)
MH49165 (NIMH)
SO PSYCHOPHARMACOLOGY, (1997 Oct) 133 (4) 383-8.
Journal code: QGI. ISSN: 0033-3158.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
EW 19980204
AB **Gamma-vinyl GABA** (GVG, also referred to as **vigabatrin**), an irreversible inhibitor of GABA transaminase (GABA-T), raises levels of GABA in nerve terminals, inhibits striatal dopamine release, and attenuates **cocaine**-induced increases in extracellular dopamine in the striatum and nucleus accumbens. In order to determine the action of GVG on dopamine-mediated reward, we examined its effects on the threshold for rewarding brain stimulation in male F-344 rats. GVG dose-dependently raised brain stimulation reward (BSR) thresholds at doses of 200, 300, and 400 mg/kg without significant effects on motor performance as measured by response latencies. In order to determine if GVG had similar modulatory effects on **cocaine**-induced lowering of BSR thresholds, the effective doses of GVG were co-administered with 2.5 and 5.0 mg/kg **cocaine**, doses that significantly lower BSR thresholds. The 400 mg/kg dose of GVG significantly blocked the lowering of thresholds seen at each dose of **cocaine**. **Cocaine** in combination with 200 or 300 mg/kg GVG, doses of GVG that significantly raise BSR thresholds, resulted in thresholds not significantly different from those obtained with **cocaine** alone. These data demonstrate that, at the doses tested, GVG is more effective at modulating basal reward thresholds that at modulating thresholds lowered by **cocaine**, implying that as dopaminergic activity increases, GABAergic activity must also increase in order to exert its inhibitory influence on dopaminergic activity.
TI **Gamma-vinyl GABA** attenuates **cocaine**
-induced lowering of brain stimulation reward thresholds.
AB **Gamma-vinyl GABA** (GVG, also referred to as **vigabatrin**), an irreversible inhibitor of GABA transaminase (GABA-T), raises levels of GABA in nerve terminals, inhibits striatal dopamine release, and attenuates **cocaine**-induced increases in extracellular dopamine in the striatum and nucleus accumbens. In order to determine the action of GVG on dopamine-mediated reward, we examined its effects on the threshold for rewarding brain stimulation in male F-344 rats. GVG dose-dependently raised brain stimulation reward (BSR) thresholds at doses of 200, 300, and 400 mg/kg without significant effects on motor performance as measured by response latencies. In order to determine if GVG had similar modulatory effects on **cocaine**-induced lowering of BSR thresholds, the effective doses of GVG were co-administered with 2.5 and 5.0 mg/kg **cocaine**, doses that

significantly lower BSR thresholds. The 400 mg/kg dose of GVG significantly blocked the lowering of thresholds seen at each dose of **cocaine**. **Cocaine** in combination with 200 or 300 mg/kg GVG, doses of GVG that significantly raise BSR thresholds, resulted in thresholds not significantly different from those obtained with **cocaine** alone. These data demonstrate that, at the doses tested, GVG is more effective at modulating basal reward thresholds that at modulating thresholds lowered by **cocaine**, implying that as dopaminergic activity increases, GABAergic activity must also increase in order to exert its inhibitory influence on dopaminergic activity.

CT Check Tags: Animal; Male; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Anticonvulsants: PD, pharmacology
*Brain: PH, physiology
***Cocaine: AI, antagonists & inhibitors**
Cocaine: PD, pharmacology
Dopamine: PH, physiology
*Dopamine Uptake Inhibitors: AI, antagonists & inhibitors
Dopamine Uptake Inhibitors: PD, pharmacology
Dose-Response Relationship, Drug
Electric Stimulation
Enzyme Inhibitors: PD, pharmacology
*GABA: AA, analogs & derivatives
GABA: PD, pharmacology
Rats
Rats, Inbred F344
*Reward
4-Aminobutyrate Transaminase: AI, antagonists & inhibitors

RN **50-36-2 (Cocaine)**; 51-61-6 (Dopamine); 56-12-2 (GABA); **60643-86-9 (vigabatrin)**

=> d l0 std bib ab hit

L13 ANSWER 10 OF 16 USPATFULL
AN 1998:61664 USPATFULL
TI Method for controlling tobacco use and alleviating withdrawal symptoms due to cessation of tobacco use
IN Viner, Norman, Ottawa, Canada
PA Synapse Pharmaceuticals International, Inc., Ottawa, Canada (non-U.S. corporation)
PI US 5760049 19980602
AI US 1997-803723 19970221 (8)
DT Utility
LN.CNT 513
INCL INCLM: 514/291.000
INCLS: 514/304.000; 514/343.000; 514/640.000; 514/813.000
NCL NCLM: 514/291.000
NCLS: 514/304.000; 514/343.000; 514/640.000; 514/813.000
IC [6]
ICM: A61K043-42
ICS: A61K031-44; A24F047-00
EXF 424/408; 424/464; 424/484; 424/492; 514/343; 514/640; 514/813; 514/291; 514/304; 131/270
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 1998:61664 USPATFULL
TI Method for controlling tobacco use and alleviating withdrawal symptoms due to cessation of tobacco use
IN Viner, Norman, Ottawa, Canada
PA Synapse Pharmaceuticals International, Inc., Ottawa, Canada (non-U.S. corporation)
PI US 5760049 19980602
AI US 1997-803723 19970221 (8)
DT Utility
EXNAM Primary Examiner: Achutamurthy, Ponnathapura
LREP Hellwege, James W.
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 513
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for controlling tobacco use and alleviating withdrawal symptoms due to the cessation of tobacco use comprising administering to a human desiring to control tobacco use and/or suffering from withdrawal due to tobacco use cessation an acetylcholine receptor antagonist and an acetylcholine esterase reactivator as active ingredients in a pharmaceutically acceptable solid matrix material capable of dissolution and/or disintegration in the mouth or the gastrointestinal tract.
SUMM Unfortunately, none of the above methods of treatment have been very successful. While such treatments may bring short-term relief to the person, long-term success has not been easily achieved. The degree of success of such methods is generally not predictable due to the fact that the degree of success achieved is dependent upon the susceptibility of the person to the particular treatment employed. In fact, it is believed that some persons are more susceptible to the effects of tobacco use than others with the result that such persons are not easily or readily able to cease such use by means of conventional treatment methods. This is particularly believed to be the case when tobacco use begins during the teenage years and continues into adulthood. Factors such as extent of tobacco use (frequency) and type of tobacco use (smoking vs. non-smoking tobacco use) play a role in the difficulty

encountered by a person upon attempting to cease or reduce the extent of tobacco use. Also, comorbid **addictions**, stress, psychiatric disorders and environmental factors may exacerbate the difficulty encountered by a particular person in ceasing tobacco use. It is believed, for example, that xenobiotic toxic agents such as pesticides, insecticides, fungicides, oxidants, solvents, heavy metals and other environmental toxins encountered by the person by various means (e.g., via drinking water and/or food impurities, etc.) may contribute to the inability of the person to cease or control tobacco use.

DETD As still yet another compound which may be administered in conjunction with one or more of the above is the inhibiting neurotransmitter gamma-aminobutyric acid (GABA) or a precursor thereof such as L-glutamic acid. GABA receptor agonists and other antiepileptics may be employed such as Epival, Baclofen, **Sabril**, barbiturates, Gabapentin, Lamotrizine and Riluzolo.

=> d 7 bib std ab hit

L13 ANSWER 7 OF 16 USPATFULL
AN 1998:128272 USPATFULL
TI Method for treating drug and alcohol **addiction**
IN Viner, Norman, Ottawa, Canada
PA Synapse Pharmaceuticals International, Inc., Ottawa, Canada (non-U.S. corporation)
PI US 5824684 19981020
AI US 1997-803722 19970221 (8)
DT Utility
EXNAM Primary Examiner: Schenkman, Leonard
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 417
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 1998:128272 USPATFULL
TI Method for treating drug and alcohol **addiction**
IN Viner, Norman, Ottawa, Canada
PA Synapse Pharmaceuticals International, Inc., Ottawa, Canada (non-U.S. corporation)
PI US 5824684 19981020
AI US 1997-803722 19970221 (8)
DT Utility
LN.CNT 417
INCL INCLM: 514/291.000
INCLS: 514/332.000; 514/343.000; 514/357.000; 514/640.000; 514/641.000; 514/811.000; 514/812.000
NCL NCLM: 514/291.000
NCLS: 514/332.000; 514/343.000; 514/357.000; 514/640.000; 514/641.000; 514/811.000; 514/812.000
IC [6]
ICM: A61K031-44
ICS: A61K031-15
EXF 514/291; 514/332; 514/343; 514/357; 514/640; 514/661; 514/811; 514/812
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating treating drug and alcohol **addiction** comprising administering to a human suffering from such **addiction** an effective amount of an acetylcholine esterase reactivator.
TI Method for treating drug and alcohol **addiction**
AB A method for treating treating drug and alcohol **addiction** comprising administering to a human suffering from such **addiction** an effective amount of an acetylcholine esterase reactivator.
SUMM The present invention is directed to a method for treatment of drug and alcohol **addiction**.

SUMM Drug and alcohol **addiction** and/or abuse is extremely common. **Addiction** is generally defined as a state of periodic or chronic intoxication detrimental to the individual which results from repeated administration of the drug. The **addicted** individual is subject to significant symptoms of withdrawal upon attempting to cease use of the **addictive** substance (whether alcohol or drugs such as **cocaine**, heroine, or conventional painkillers).

SUMM A number of medical therapies have been tried with differing success in the treatment of alcohol and drug **addiction**. See, for example,

U.S. Pat. Nos. 4,786,653; 4,847,281; 4,919,916; 4,935,429; 4,942,182; 4,948,803; 4,956,391; 5,028,611; 5,051,426; 5,059,600; 5,075,341; 5,083,129; 5,102,913; 5,114,942; 5,130,388; 5,180,729; 5,185,329; 5,189,064; 5,223,497; 5,232,934; 5,397,782; 5,462,948; and 5,556,837.

SUMM The potential effect of xenobiotic toxins (such as pesticides, fungicides, solvents, heavy metals, food additives, etc. as well as other environmental contaminants) has not been well-studied in relation to the occurrence and severity of alcohol and **drug addiction** and/or **abuse**.

SUMM It is accordingly an object of the present invention to provide a method for treating drug and alcohol **addiction**.

SUMM In accordance with the present invention, there is accordingly provided a method for treating drug and alcohol **addiction** comprising administering to a human suffering from or subject to such **addiction** an effective amount of an acetylcholine esterase reactivator.

SUMM The present invention involves the administration to a person suffering from a drug or alcohol **addiction** an effective amount of an acetylcholine esterase reactivator.

SUMM **Addictions** which are suitable for treatment by the method of the present invention include alcohol **addiction**, as well as **addictions** of a variety of drugs, including **cocaine**, heroin, as well as more conventional drugs such as painkillers. This list is not all inclusive and other drug **addictions** are suitable for treatment.

DETD Acetylcholine esterase reactivators (such as 2-PAM and HI-6) have been used in conjunction with acetylcholine receptor antagonists (such as atropine) to provide in vivo protection against nerve gas agents and other organophosphate poisons. See, for example, U.S. Pat. Nos. 3,063,901; 4,713,391; 4,865,837; and 4,925,856. Atropine (an acetylcholine receptor antagonist) has also been used to treat bronchitis, nasal inflammation, hay fever, etc. as discussed in U.S. Pat. No. 1,794,292. However, an acetylcholine esterase reactivator such as oximes has not previously been employed to alleviate the symptoms of alcohol and **drug abuse** and/or **addiction**.

The amounts of the respective components required to provide the benefits of the present invention are orders of magnitude less than the amounts normally administered to provide protection against nerve gas agents or toxic organophosphate poisoning.

DETD As still yet another compound which may be administered in conjunction with one or more of the above is the inhibiting neurotransmitter gamma-aminobutyric acid (GABA) or a precursor thereof such as L-glutamic acid. GABA receptor agonists and other antiepileptics may be employed such as Epival, Baclofen, **Sabril**, barbiturates, Gabapentin, Lamotrizine and Riluzole.

DETD The acetylcholine esterase reactivator and the acetylcholine receptor antagonist are employed or administered in an amount effective to reduce or prevent symptoms of alcohol and **drug abuse** and/or **addiction**. The phrase "reduce or prevent" is intended to refer to any degree of reduction of the symptoms suffered by the person.

CLM What is claimed is:

1. A method for treating drug and alcohol **addiction** comprising administering to a human suffering from drug and alcohol **addiction** an acetylcholine esterase reactivator in an amount

effective to treat such **addiction**.

14. The method of claim 1 wherein said human suffers from alcohol **addiction**.

15. The method of claim 1 wherein said human suffers from drug **addiction**.